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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/692,824	10/23/2003	John Langenfeld	54704.8036.US03 RWJ-01-02	1322

7590 04/27/2005

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EXAMINER	
RAWLINGS, STEPHEN L	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 04/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/692,824	LANGENFELD, JOHN	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,14,16 and 18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,14,16 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20041103*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The preliminary amendment filed March 9, 2005 is acknowledged and has been entered. Claims 2-13, 15, 17, 19, and 20 have been canceled. Claims 1 and 16 have been amended.

2. Claims 1, 14, 16, and 18 are pending in the application and currently under prosecution.

Information Disclosure Statement

3. The information disclosure filed November 1, 2004 has been considered. An initialed copy is enclosed.

Priority

4. Applicant has claimed benefit of the earlier filing date of copending U.S. Application No. 10/044,716, filed January 11, 2002, which, in turn, claims benefit of U.S. Provisional Application No. 60/261,252, filed January 12, 2001.

Applicant, however, has not complied with one or more conditions for receiving the benefit of the earlier filing dates of the provisional application under 35 U.S.C. § 120 for the following reason:

To receive benefit of the earlier filing date under 35 USC § 120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. § 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The specification of copending U.S. Application No. 10/044,716, filed January 11, 2002, fails to provide an enabling disclosure of the invention claimed

in the instant application. Although the prior application discloses that bone morphogenetic protein-2 (BMP-2) apparently enhances formation of blood vessels around a tumor in a nude mouse (see, e.g., paragraph [0046]), there is no showing, prophetic or otherwise, that the inhibition of an activity of BMP-2 reduces vascularization of a tumor. It follows that the specification of the prior application provides no factual evidence that the invention claimed in the instant application can be used to reduce the vascularization of a tumor in a subject. There is a disclosure of an experimental strategy for determining the effect of BMP-2 and noggin tumor vasculature in vivo (paragraph [0142]), but as there is no disclosure of results acquired from such experiments, it appears that the experimental data did not become available until after the filing date.

Furthermore, Applicant filed an amendment in the prior application on June 25, 2002, which sought to amend the specification at page 30 in paragraph [0089] to recite the following after the second sentence:

> These separated RT-PCR products were not sequenced, however, and the "BMP-2 primers" used were potentially capable of amplifying both BMP-2 and BMP-4, which are highly homologous. Thus, this data alone cannot be definitively interpreted as showing amplification of BMP-2 in the absence of sequencing data.

Then, at page 2 of that amendment, Applicant remarked that subsequent sequencing of the RT-PCR products revealed amplification of BMP-4 rather than BMP-2.

Because the primers used to amplify the nucleic acids encoding BMP-2 were potentially capable of amplifying both BMP-2 and BMP-4, as Applicant would apparently agree, the data presented in the prior application cannot be definitively interpreted as showing amplification of BMP-2 in the absence of sequencing data. Moreover, as Applicant has provided an admission that BMP-4 is amplified using the disclosed primers, as opposed to BMP-2, the prior application should not be considered to have to provide a reasonably enabling disclosure of the invention claimed in the instant application.

In addition, because the present application discloses that the anti-BMP-2 antibody "MAB355" cross-reacts with BMP-4 (paragraph [0219]), and as it

appears that this same antibody was used in the experiments disclosed in the specification of the prior application (see, e.g., paragraph [0141]), the results of the Western analyses disclosed in the prior application cannot be taken as factual evidence that BMP-2, as opposed to BMP-4, is overexpressed in the cancer cell lines and lung cancer specimens tested. Only in the present application does Applicant disclose that an antibody (MAB3551) that binds specifically to BMP-2, which does not cross-react with BMP-4, was used to determine the presence of BMP-2 in the cell lines and specimens (paragraph [0141]).

Accordingly, the effective filing date of the instant claims is considered to be the date that the present application was filed, namely October 23, 2003.

Specification

5. The specification is objected to because the use of numerous improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Examples of such improperly demarcated trademarks include Kodak™ (paragraph [00165]), Trizol™ (paragraph [00166]), and ABI Prism™ (paragraph [00166]).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

6. The specification is objected to because of the following informality: The misspelling of "ABI Prism™" as "IBI Prism™" at page 66 (paragraph [00166]).

7. The disclosure is objected to because the disclosure refers to embedded hyperlinks and/or other forms of browser-executable code and to the Internet contents so identified. Reference to hyperlinks and/or other forms of browser-executable code and to the Internet contents so identified is impermissible and therefore requires deletion.

At page 86, for example, the specification references www.cancer.org, which is impermissible.

The attempt to incorporate essential or non-essential subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP § 608.01(p), paragraph I regarding acceptable incorporation by reference. See 37 CFR § 1.57.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1, 14, 16, and 18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the

published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description'' Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

The claims are drawn to a method for treating a tumor (i.e., reducing vascularization of a tumor) comprising administering to a subject a therapeutically effective amount of a "BMP-2 activity inhibitor", or more particularly a therapeutically effective amount of an expression vector having a nucleic acid sequence encoding a "BMP-2 activity inhibitor".

At page 6, paragraph [0017], through page 7, paragraph [0019], for example, the specification describes the "BMP-2 activity inhibitor" as a polypeptide that binds BMP-2, a polypeptide that binds a receptor of BMP-2, an antibody that binds specifically to BMP-2, an antisense oligonucleotide that inhibits the expression of a nucleic acid encoding BMP-2, a known antagonist of BMP-2, such as noggin, chordin, Cerberus 1 homolog, gremlin, and 2-deoxy-2,3-didehydro-D-N-acetylneuramic acid (DAN), and a fragment of such known antagonists.

The structural and functional variability of the members of the genus of agents that are capable of inhibiting an activity of BMP-2 is evident upon consideration of the disparate structures and functions of the various different types of molecules or compounds that are used in practicing the invention (e.g., an antisense oligonucleotide vs. an antibody vs. a ligand of BMP-2 vs. a small organic molecule). This variability is further evident upon consideration of the disparate structures and functions of the known, naturally occurring inhibitors of an activity of BMP-2 (e.g., noggin, gremlin, etc.), which are described as useable in practicing the invention.

Consequently, given the broadest reasonable interpretation, the claims are directed to a genus of agents (i.e., "BMP-2 activity inhibitors") that differ both structurally and functionally, despite having the common ability to reduce an apparent activity of the BMP-2 in a patient treated using the claimed invention.

Notably, the specific activity of BMP-2 that is inhibited by the members of this genus of agents is not described. It follows therefore that claims are directed to a genus of agent capable of inhibiting any apparent activity of BMP-2 that is measurable or determinable by any number of assays that describe any one of its many biologic functions (e.g., the ability to bind a receptor of BMP-2; the ability to bind noggin; the ability of BMP-2 to bind gremlin; or the ability of BMP-2 to bind DAN).

However, apart from naturally occurring inhibitors of BMP-2 (e.g., noggin) and DAN that were already known, the specification does not adequately describe the members of the genus of agents capable of inhibiting an activity of BMP-2, such that the skilled artisan could immediately envision, recognize, or distinguish at least a substantial number.

Moreover, as disparate are the chemical structures and functions of the various different types of agents, the prior art teaching such agents, then, constitutes factual evidence that the skilled artisan could not immediately reasonably conclude that Applicant had possession of the claimed invention at the time the application was filed, because the specification necessarily fails to describe any particularly identifying (i.e., substantial) *structural* feature that is commonly shared by the agents capable of inhibiting an activity of BMP-2, which might permit the skilled artisan to envision, recognize, or distinguish these and other members of the genus of agents to which the claims are directed. For example, an antibody and an antisense oligonucleotide share no substantial structural feature, if any at all, that correlates with their ability to inhibit an activity of BMP-2. Neither the antibody nor the antisense oligonucleotide share a substantial structural feature with the few adequately described agents (e.g., noggin) that are capable of inhibiting an activity of BMP-2 and which are therefore useable in practicing the invention; and as a final example, an antibody that binds a receptor of BMP-2 and an antibody that binds BMP-2, although both are perhaps capable of inhibiting the ability of BMP-2 to bind the receptor, share no common particularly identifying structural feature that is essential to that

capability, since the antibodies comprise functionally distinct antigen-binding domains.

With further regard to those agents that are adequately described, namely the naturally occurring protein inhibitors of an BMP-2 activity (Noggin, Chordin, Cerberus 1 homolog, and Gremlin) and a small organic molecule inhibitor (DAN), again, as the structures and functions of these ligands of BMP-2 vary considerably, there is no disclosed or known structural feature, which is particularly identifying of those proteins or that is shared by at least most of those proteins, that correlates with their common ability to inhibit an activity of BMP-2. Accordingly, these proteins are not representative of each other, nor of the genus of agents to which the claims are directed, which have the ability to inhibit an activity of BMP-2 to achieve therapeutic effect in treating cancer, or more particularly in reducing vascularization of a tumor in a subject.

Furthermore, the Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See *Noelle v. Lederman*, 69 USPQ2d 1508 1514 (CA FC 2004) (citing *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568). As discussed in greater detail below in the rejection of claims as lacking an enabling disclosure, there is in fact such unpredictability.

As the claims encompass the use of fragments of these naturally occurring proteins and small organic molecules to treat cancer, it is duly noted that the supporting disclosure does not describe which fragments of noggin, or any of the other proteins, or of DAN are capable of inhibiting an activity of BMP-2. "[G]eneralized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004). In this instance, as in that, there is no language that adequately describes fragments of the known inhibitors of a BMP-2 activity that can be used to achieve the claimed therapeutic effect. A description of what a

material does, rather than of what it is, does not suffice to describe the claimed invention.

While the written description requirement can by satisfied without an actual reduction to practice, the disclosure of a catalog of potentially effective substances that might be found to be useful in practicing the claimed invention does not fulfill the written description requirement. Recognizing that the claims are drawn to a method comprising administering to a patient an unspecified substance, or an expression vector encoding such a substance having the ability to inhibit an activity of BMP-2, it is aptly noted that the Federal Circuit has decided that a generic statement that defines a genus of substances by *only* their functional activity, i.e., the ability to inhibit an activity of BMP-2 to achieve therapeutic effect, does not provide an adequate written description of the genus. See *The Reagents of the University of California v. Eli Lilly*, 43 USPQ2d 1398 (CAFC 1997). The Court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a precise definition of a representative number of members of the genus, such as by reciting the structure, formula, chemical name, or physical properties of those members, rather than by merely reciting a wish for, or even a plan for obtaining a genus of molecules having a particular functional property. The recitation of a functional property alone, which must be shared by the members of the genus, is merely descriptive of what the members of genus must be capable of doing, not of the substance and structure of the members.

Although *Lilly* related to claims drawn to genetic material, the statute applies to all types of inventions. "Regardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to the subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods". *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1984 (CAFC 2004). The

claimed method depends upon finding a compound that has the ability to inhibit an activity of BMP-2 to achieve therapeutic effect in treating cancer, and more particularly in reducing vascularization of tumors, using the claimed process; without such a compound, it is impossible to practice the invention.

In addition, although the skilled artisan could potentially identify agents that might be used in practicing the claimed invention by screening for substances that are capable of inhibiting an activity of BMP-2 to achieve therapeutic effect in treating cancer, it is duly noted that the written description provision of 35 U.S.C § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*.

Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

Absent the adequate description of a representative number of members of the genus of agents to which the claims are directed, the supporting disclosure amounts to no more than a mere invitation to identify a substance that can be used as an agent for treating cancer and reducing vascularization of tumors by inhibition of an activity of BMP-2.

Finally, Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description'' Requirement (66 FR 1099-1111, January 5, 2001) states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing

distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims encompass a genus of substances having the ability to inhibit an activity of BMP-2 to achieve therapeutic effect in the treatment of cancer, which vary both structurally and functionally, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. In this instance, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; Applicant has not shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; and Applicant has not described distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention at the time the application was filed.

Notably the Federal Circuit has recently decided that the description of a fully characterized molecular target of an antibody is sufficient to adequately describe an antibody that binds that target. See *Noelle v. Lederman*, 69 USPQ2d 1508 (CA FC 2004). However, the same court decided that each case involving the issue of written description, "must be decided on its own facts. Thus, the precedential value of cases in this area is extremely limited." *Vas-Cath*, 935 F.2d at 1562 (quoting *In re Driscoll*, 562 F.2d 1245, 1250 (C.C.P.A. 1977)). In that instance, the claims are directed to an antibody that inhibits an activity of BMP-2 or an expression vector encoding such an antibody. BMP-2, for example, is a fully characterized antigen; were the claims directed to an antibody that binds BMP-2, the written description would be met by the description of the fully characterized antigen alone. However, in this instance, the claims are not directed to an antibody that merely binds its molecular target, but rather to an antibody that binds to its molecular target and thereby inhibits an activity of BMP-2 to produce a therapeutic effect in a patient diagnosed with cancer. While the

particular activity of BMP-2 that is inhibited is not specified in the claims, nor limited by the supporting disclosure, an antibody that binds BMP-2 is not reasonably expected to inhibit an activity of BMP-2, since some antibodies are expected to bind without consequence, while others are expected to bind and either stimulate or inhibit that activity. Moreover, some antibodies that bind BMP-2 are expected to inhibit the growth of cancer cells, while others are expected to have either no effect or to actually promote their growth. This assertion is supported, for example, by the teachings of Stancoviski et al. *(Proceedings of the National Academy of Science USA.* 1991; **88**: 8691-8695). Stancovski et al. characterizes the effects upon the growth of tumor cells of various different antibodies that each bind the extracellular domain of a tumor-associated antigen, ErbB2; see entire document (e.g., the abstract). Stancovski et al. teaches some anti-ErbB2 antibodies inhibited tumor cell growth, but others actually accelerated their growth (page 8693, column 1). Furthermore, as explained below in the rejection of the claims as lacking an enabling disclosure, the role of BMP-2 in cancer cells varies, such that the inhibition of its activity can either inhibit or promote the growth of cancer in a patient. Accordingly, the mere generalized description of antibodies that bind and inhibit an activity of BMP-2, although a fully characterized antigen, cannot suffice to describe antibodies that have a therapeutic effect, because the skilled artisan could not immediately envision, recognize, or distinguish antibodies that bind BMP-2 to inhibit an activity thereof, which have therapeutic effect (e.g., inhibit the growth of cancer cells), from such antibodies that lack therapeutic effect (e.g., promote the growth of cancer cells). Here, the specification does not exemplify the use of an antibody that binds to BMP-2 and thereby inhibits an activity of the protein to produce a therapeutic effect in a subject diagnosed with cancer, nor is there reference to a deposit of such an antibody or a description of its chemical structure, so there is no factual evidence suggesting that Applicant had possession of such an antibody capable of inhibiting an activity of BMP-2 and thereby causing a therapeutic effect at the time the application was filed. It should be noted that the foregoing discussion is

intended to be exemplary, as the claims are not limited to a method comprising administering an antibody that binds BMP-2. It stands to reason that not all of the molecular targets of a therapeutic antibody, which might be useful in practicing the claimed process, have been identified and fully characterized.

10. Claims 1, 14, 16, and 18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The amount of guidance, direction, and exemplification set forth in the supporting disclosure is not reasonably commensurate in scope with the claims, nor is it sufficient to enable the skilled artisan to practice the claimed process without undue experimentation.

Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). These factors include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

As explained above in the rejection of the claims as lacking a sufficient description in the supporting disclosure, the claims are directed to a genus of structurally and functionally different molecules or compounds that inhibit an activity of BMP-2. However, proteins, such as BMP-2, are multifunctional, and the specific activity that is inhibited by the members of the genus of molecules and compounds to which the claims are directed is not specified, nor is it described in a limiting manner elsewhere in the specification. The molecules and compounds include such highly disparate molecules as antibodies, antisense

oligonucleotides, and small organic molecules; yet, the only members of the genus that are adequately described are a few naturally occurring proteins that are known inhibitors of an activity of BMP-2, such as noggin, and one small organic molecule (DAN). However, apart from the procurement of noggin from a commercial source, the production of molecules and compounds that are used in practicing the claimed invention is not exemplified.

The claims specifically encompass the use of fragments of the naturally occurring proteins that inhibit an activity of BMP-2 (e.g., human noggin) and the small organic molecule inhibitor DAN. However, the specification does not teach which fragments of these proteins or of DAN are capable of inhibiting an activity of BMP-2. Moreover, it fails to describe which portions of the amino acid sequence are essential to the ability of the protein inhibitors to inhibit any particular activity of BMP-2.

The claims are drawn to a method for treating cancer in a patient; and more particularly reducing vascularization of tumors in the patient; however, the use of claimed invention to treat cancer in a patient is not exemplified in the specification. The specification only shows that subcutaneous *co-injection* of agarose beads coated with recombinant mouse noggin and A549 lung cancer cells reduced the growth of the resulting tumor in nude mice; see, e.g., paragraph [00190]. It does not show that noggin directly inhibits angiogenesis *in vivo*. As the claimed invention cannot be practiced in the "real world" by co-injecting the "BMP-2 activity inhibitor" together with the tumor cells to be treated in a patient, the claimed invention has not been exemplified. Moreover, the claimed invention has not been shown to produce a therapeutic effect (i.e., reduce vascularization of tumors) in a patient diagnosed with an established tumor.

Although most of the claims are not specifically limited to any one type of cancer, the specification discloses that in particular the invention is used to treat lung cancer, bladder cancer, breast cancer, colon cancer, kidney cancer, ovarian cancer, thyroid cancer, endometrial cancer, omental cancer, testicular cancer, and liver cancer; see, e.g., paragraph [0016]. The specification, however, only

shows that noggin can reduce the growth of lung cancer cells injected subcutaneously in nude mice.

Much of that disclosed in the present application has been published. Langenfeld et al. (*Carcinogenesis*. 2003; **24** (9): 1445-1454) teaches that BMP-2, but not BMP-4 is overexpressed in non-small cell lung cancer cells, as compared to normal lung cells or benign tumor cells of the lung; see entire document (e.g., the abstract). Langenfeld et al. shows that ectopic, enforced expression of BMP-2 in a A549 lung cancer cell line enhanced the growth of tumors in nude mice inoculated with these cells; see, e.g., the abstract. Langefeld et al. teaches inhibition of BMP-2 activity by recombinant noggin or an antibody that binds BMP-2 significantly reduced this tumor growth; see, e.g., the abstract. However, as in the disclosed examples, the inhibitors were *co-injected* with the A549 lung cancer cells (page 1447, column 1). Langenfeld et al. concludes that these data demonstrate that BMP-2 *may* have important biological activity in human lung carcinomas but cautions that "[f]urther studies are needed to define the specific mechanisms activated by BMP-2 in human carcinomas" (page 1453, column 1).

Notwithstanding, Applicant is reminded that supporting documents cannot be relied upon to correct the deficiencies of the specification by supplying the necessary and essential teachings, guidance, and exemplification that the specification lacks. See MPEP § 2164.05(a).

More recently Langenfeld and colleagues have published an additional report (Langenfeld et al., *Molecular Cancer Research.* 2004 Mar; 2: 141-149) that discloses although BMP-2 is highly overexpressed in the majority of patient-derived lung carcinomas, a mechanism revealing its role in cancer has not been established; see entire document (e.g., the abstract). Similarly, Langenfeld et al. disclose that the role of BMP family members in vascular development has not been extensively studied (e.g., page 145, column 1); however, Langenfeld et al. discloses results that they conclude show that inhibition of BMP-2 by noggin or antisense transfection decreases the lung tumor vasculature in their nude mouse model (e.g., page 145, column 2). Thusly, Langenfeld et al. discloses a study

that furthers our understanding of the role of BMP-2 in lung cancer; it is however apparent that our understanding is not yet complete (e.g., page 146, column 2, through page 147, column 1). In particular, Langenfeld et al. discloses that while the inhibition of BMP-2 activity by noggin in A549 lung cancer cells appears to inhibit the growth of the tumor in nude mice, other studies have demonstrated quite paradoxically that the inhibition of BMP-2 activity in different types of tumor cells may actually promote their growth (page 147, column 1).

Indeed, Tada et al. (*Oncol. Rep.* 1998 Sep-Oct; **5** (5): 1137-1140), for example, have reported that treatment of the same A549 lung cancer cells used by Langenfeld and colleagues in their studies with BMP-2 resulted in *inhibition* of their growth in anchorage-dependent and independent growth conditions; see entire document (e.g., the abstract). Accordingly, the skilled artisan might reasonably conclude that inhibiting the activity of BMP-2 by, for example, exposing tumor cells to noggin would not be therapeutic, since it would to the contrary be expected that inhibiting BMP-2 might actually promote the growth of the tumor.

Just how the opposing conclusions of Langenfeld et al. and Tada et al. might be reconciled is not known, but the need to further clarify the role of BMP-2 in tumorigenesis before practicing the claimed invention is apparent.

Still others have reported that BMP-2 has an inhibitory role, rather than a stimulating role, in lung carcinogenesis. For example, Buckley et al. (*Am. J. Physiol. Lung Cell Mol. Physiol.* 2004; **286**: L81-L86) have disclosed results that they conclude show that BMP-2 suppresses the transformed phenotype of A549 cells in vitro; see entire document (e.g., the abstract). Similarly, Buckley et al. reports that BMP-4 can induce senescence and thus negatively regulate the growth of A549 lung cancer cells (e.g., abstract). Again, the results published by Buckley et al. would suggest that contrary to the assertions set forth in the instant application, the inhibition of BMP-2 would not be therapeutic.

While Langenfeld and colleagues have concluded that BMP-2 promotes angiogenesis, since, e.g., its inhibition diminished blood vessel formation

(Langenfeld et al. 2004, *supra*; e.g., abstract), and therefore promotes tumorigenesis, other investigators have posed that BMP-2 has a role in preventing cancer. Hardwick et al. (*Gastroenterology*. 2004 Jan; **126** (1): 111-121), for example, concludes that BMP-2 acts as a tumor suppressor, since their study shows the protein promotes apoptosis and differentiation and inhibits proliferation of mature colonic epithelial cells; see entire document (e.g., the abstract). In fact, Hardwick et al. discloses that expression of the gene encoding BMP-2 in dysplastic epithelial cells of microadenomas acquired from patients genetically predisposed to colorectal cancer is lost (page 118). Contrary to the presumed utility of administering to a patient diagnosed with cancer an inhibitor of BMP-2 activity, which asserted in this application, Hardwick et al. discloses that administering noggin to mice led to reduced apoptosis of colon cells; see, e.g., page 117, Figure 7. Hardwick et al. concludes, as loss of BMP signaling appears to lead to decreased apoptosis, its loss would be expected to be associated with increased carcinogenesis (page 120). Similarly, Haramis et al. (*Science*. 2004 Mar 12; **303**: 1684-1686) published the results of a study that they conclude shows that loss of BMP-4 activity leads to colon polyp growth and ultimately neoplasia (i.e., cancer); see entire document (e.g., the abstract). Haramis et al. discloses that inhibiting BMP signaling by noggin results in the formation of cellular structures in the colonic crypts, which mirror those that occur in patients predisposed to cancer by the syndrome juvenile polyposis (e.g., abstract). More recently, Nishanian et al. (Biochem. Biophys. Res. Com. 2004; 323: 91-97) teaches that inactivation of BMP signaling by mutation of a BMP receptor actually causes familial juvenile polyposis; see entire document (e.g., the abstract).

In other types of cancer, too, including, for example, breast cancer cells, BMP-2 has been reported to act as an antiproliferative agent. For example, Ghosh-Choudhury et al. (*Biochem. Biophys. Res. Com.* 2000; **272**; 705-711) discloses that BMP-2 dose-dependently inhibits the growth of MDA MB 231 human breast cancer cells; see entire document (e.g., the abstract). By way of

mechanism, Ghosh-Choudhury et al. discloses that BMP-2 treatment arrests the cells in the G1 phase of the cell cycle, perhaps as a result of causing the hypophosphorylation of the retinoblastoma protein (Rb) and increasing the expression of the tumor suppressor p21 (e.g., abstract). Apparently, BMP-2 also causes hypophosphorylation of Rb and increases expression of p21 in prostate cancer cells, which Tomari et al. (*Int. J. Mol. Med.* 2005 Feb; **15** (2): 253-258) teaches may explain how BMP-2 inhibits their proliferation; see entire document (e.g., the abstract). Still others (e.g., Nakamura et al. (*Biochem. Biophys. Res. Com.* 2003; **307**: 206-213) and Wen et al. (*Biochem. Biophys. Res. Com.* 2004; **316**: 100-106)) have shown that BMP-2 acts to suppress the growth of gastric and brain cancer cells.

Accordingly, given that the role of BMP-2 in cancer has not yet been fully characterized, and contrary to the implications of the data disclosed in the instant application, most reports suggest that its role is to inhibit tumorigenesis, the skilled artisan could not use the claimed invention without undue experimentation. It is not clear that the inhibiting an activity of BMP-2 should be reasonably expected to be therapeutic in the treatment of cancer.

Furthermore, one cannot extrapolate the teachings of the specification to the enablement of the invention, particularly in the absence of exemplification that is commensurate in scope with the claims, because it is well known that the art of drug discovery for is highly unpredictable. With particular regard to anticancer drug discovery, Gura (*Science.* 1997; **278**: 1041-1042), for example, teaches that researchers are faced with the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile (abstract). Because of a lack of predictability, Gura discloses that often researchers merely succeed in developing a therapeutic agent that is useful for treating the animal or cell that has been used as a model, but which is ineffective in humans, and indicates that the results acquired during pre-clinical studies are often non-correlative with the results acquired during clinical trials (page 1041, column 2). Gura very succinctly teaches our lack in ability to reliably

extrapolate pre-clinical data to accurately predict the outcomes of such treatments in humans is due to the fact that "xenograft tumors don't behave like naturally occurring tumors in humans" (page 1041, column 2). Gura teaches that although researchers had hoped that xenografts would prove to better models for studying cancer in humans and screening candidate therapeutic agents for use in treating patient diagnosed with cancer, "the results of xenograft screening turned out to be not much better than those obtained with the original models". Gura states that as a result of their efforts, " '[w]e had basically discovered compounds that were good mouse drugs rather than good human drugs' ".

Although the teachings of Bergers et al. (*Current Opinion in Genetics and Development.* 2000; **10**: 120-127) are drawn to specific antitumor agents, namely matrix metalloproteinase inhibitors, the great extent of unpredictability in the art is underscored by their disclosures. Bergers et al. teaches, "a body of data over the past few years indicate [...] that proteinases and proteinase inhibitors may, under special circumstance, either favor or block tumor progression. For example, ectopic expression of TIMP-1 [a natural inhibitor of metalloproteinases] allows for some tumors to grow, while inhibiting others" (page 125, column 2). In fact, Bergers et al. discloses that the Bayer Corporation recently halted a clinical trial of a metalloproteinase inhibitor because patients given the drug experienced greater progression of cancer than did patients given a placebo (page 125, column 1). Bergers et al. comments, "these results are somewhat surprising and contrary to Bayers' preclinical data, which confirmed that the drug inhibited tumor activity in rodents" (page 124, columns 1-2). Bergers et al. also teaches that the absence of a metalloproteinase activity in mice actually predisposes the mice to *de novo* squamous carcinomas. Thus, the skilled artisan cannot accurately and reliably predict the effect of administering a pharmaceutical composition comprising an agent purported to have a desired pharmacological effect to a subject. Always the therapeutic effectiveness or efficacy of any unproven drug regimen can only be determined empirically. Therefore, it is submitted that if the specification is to be considered reasonably enabling of the claimed invention in

such an unpredictable art as this, there should be working exemplification or the disclosure of the results of pre-clinical studies that are predictive of the outcome that will be achieved in its clinical application, which is reasonably commensurate in scope with the indicated uses of the claimed invention, as recited in the claims. Otherwise, the skilled artisan could not make and/or use the claimed invention without the need to first perform such undue experimentation.

As the claims are specifically directed to methods comprising delivery of an expression vector encoding an inhibitor of BMP-2, the claims read on treatment processes termed in the art as "gene therapy".

The art of gene therapy, i.e., the *in vivo* delivery genetic information to targeted cells within a body using naked DNA or viral vectors or by reintroducing *ex vivo* modified host cells into the body, is still in its infancy. Moreover, the art is highly unpredictable and its successful application has been hindered by numerous limitations, which the specification does not remedy and would preclude the skilled artisan from having a reasonable expectation of successfully making and using the claimed invention without undue experimentation.

For example, the teachings of the specification have not overcome the problems with *in vivo* delivery and expression. Verma et al. (*Nature* 1997, **389**: 239-242) teaches that the Achilles heel of gene therapy is gene delivery (page 239, column 3). Verma et al. states that the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression; see entire document (e.g., page 239, column 3). Similarly, Amalfitano et al. (*Current Gene Therapy* 2002, **2**: 111-133) teaches that non-viral mediated transfer of DNA generally suffers from low transduction efficiencies; see entire document (e.g., page 111, column 2). In addition, Amalfitano et al. discusses numerous limitations that have been encountered in using retroviral vectors to deliver DNA into a subject and teaches the use of adenoviral vectors can be ineffective because of the induction of strong immune responses in the host to the viral vectors and direct acute and chronic toxicity caused by the vector itself; see entire document (e.g., abstract).

It is noted that Amalfitano et al. teaches that a despite general lack of success, the first conclusive evidence that gene therapy can show efficacy in humans was achieved in human X-linked SCID subjects *via* retrovirus transduction (page 111, column 2). However, since the publication, The Department of Health and Human Services has released a memorandum dated January 14, 2003, a copy of which is attached to this Office action, that urges all such investigations to be discontinued until new data are available, the possible etiology and risks of adverse events associated are considered, and recommendations emerge. Despite the initial promise of the trial studying gene transfer as a possible treatment for the disease, investigators have found that retroviral-mediated insertion of the transgene has caused the subjects to develop cancer. The results of the trial underscore the high degree of unpredictability associated with the art and the fact that the skilled artisan could not make or use the claimed invention with a reasonable expectation of success without need to perform additional and an undue amount of experimentation.

The state of the art, as a whole, is well defined by Pandha et al. (*Current Opinion in Investigational Drugs* 2000; **1** (1): 122-134). Pandha et al. teaches:

> Despite the rapid technological advances that continue to sustain the field of cancer gene therapy, few individual patients have benefited from the revolution so far. The plethora of clinical trials described confirms that each malignancy will have its own ideal strategy based on the associated molecular defects, and there has been rapid progress from this viewpoint. At the same time, there has been a renewed appreciation for the limitations to gene therapy, which include low efficiency of gene transfer, poor specificity of response and methods to accurately evaluate responses, and lack of truly tumor-specific targets at which to aim. As with all new therapies, we are climbing a steep learning curve in terms of encountering treatment-related toxicities, as well as profound ethical and regulatory issues (abstract).

As the disclosure teaches that the gene encoding BMP-2 is expressed in lung cancer, in particular, it is noted that Ferrari et al. (*Clin. Exp. Immunol.* 2003; **132**: 1-8), for examples, addresses the immunological hurdles to lung gene therapy, which continue to hinder the successful clinical application of such treatments and yet which have not been resolved by the instant disclosure; see entire document (e.g., the abstract). Ferrari et al. teaches that although gene transfer to the lung is feasible, gene expression from both viral and non-viral

vectors has been inefficient and inflammatory, antibody, and T cell responses limit transgene expression duration and readministration (abstract), just as earlier published references also indicate. So, despite advancements in the art of gene therapy, the same limitations that hindered its successful therapeutic application in past years continue to hamper its clinical use today.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

In deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997).

The specification does not teach the skilled artisan to use at least a substantial number of embodiments encompassed by the claims, nor does it teach the skilled artisan to make at least a substantial number of the "BMP-2 activity inhibitors" to which the claims are directed. The skilled artisan cannot predict whether any given embodiment can be used successfully to treat cancer and in particular reduce vascularization of tumors *in vivo*; nor can the skilled artisan predict the structures of the "BMP-2 activity inhibitors" that are used in practicing the claimed invention. Rather, the skilled artisan can only identify embodiments of the claimed process that can be used to treat cancer by empirically testing the effectiveness of the process; and one cannot make or use the "BMP-2 activity inhibitors" without first determining which activities of BMP-2 can and should be inhibited to have the desired therapeutic effect and then designing and/or isolating and testing candidate "BMP-2 activity inhibitors" that are expected to cause such therapeutic effects. Therefore, amount and nature of

the experimentation that would need be performed before the claimed invention could be used falls well into the realm of undue experimentation.

Thus, the overly broad scope of the claims would merely serve as an invitation to one skilled in the art to identify "BMP-2 activity inhibitors" that produce the desired therapeutic effect in a patient diagnosed with cancer; yet, defining a substance by its principal biological activity amounts to an alleged conception having no more specificity than that of a wish to know the identity of any material with that biological property. See *Colbert v. Lofdahl*, 21 USPQ2d 1068, 1071 (BPAI 1991).

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with *Ex parte Forman*, 230 USPQ 546 (BPAI 1986), the amount of guidance, direction, and exemplification contained in the supporting disclosure would not be sufficient to enable the skilled artisan to use the claimed invention without undue experimentation.

Conclusion

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
April 19, 2005